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Polypharmacy and falls in the middle age and elderly population

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Aim
Falls in the elderly are common and often serious. We studied the association between multiple drug use (polypharmacy) and falls in the elderly.

Methods
This was a population-based cross-sectional study, part of the Rotterdam Study. The participants were 6928 individuals aged ≥55 years. The prevalence of falls in the previous year was assessed. Medication use was determined with an interviewer-administered questionnaire with verification of use. Polypharmacy was defined as the use of four or more drugs per day.

Results
The prevalence of falls strongly increased with age. Falls were more common in women than in men. Fall risk increased with increasing disability, presence of joint complaints, use of a walking aid and fracture history. The risk of falling increased significantly with the number of drugs used per day (P for trend <0.0001). After adjustment for a large number of comorbid conditions and disability, polypharmacy remained a significant risk factor for falling. Stratification for polypharmacy with or without at least one drug which is known to increase fall risk (notably CNS drugs and diuretics) disclosed that only polypharmacy with at least one risk drug was associated with an increased risk of falling.

Conclusions
Fall risk is associated with the use of polypharmacy, but only when at least one established fall risk-increasing drug was part of the daily regimen.

Introduction

Falls are a common phenomenon in the elderly and are associated with considerable morbidity and mortality [1]. They often lead to reduced functioning and to nursing home admissions [2]. The risk of falling increases dramatically with the number of risk factors, such as musculoskeletal problems, neurological diseases, psychosocial characteristics, functional dependency and drug use.

Polypharmacy, usually defined as the use of more than three or four medications, is regarded as an important risk factor for falling in the elderly [3–7]. A meta-analysis [6, 7] showed an increased fall risk in users of diuretics, antiarrhythmics and psychotropics. However, in a large population-based study it was concluded that comorbidity, being a relevant recognized risk factor for falling in the elderly, fully explains the increased risk associated with drug use [8].

Our hypothesis was that drugs can be an independent risk factor for falling but that polypharmacy itself is not

a risk factor. In our hypothesis the association between polypharmacy and falling is explained by a higher probability of receiving a risk-increasing drug with the number of drugs taken. To investigate this issue, we assessed the association between polypharmacy and falling.

Methods

This cross-sectional analysis was part of the Rotterdam Study, a population-based prospective cohort study of 7983 people aged 55 years (mean age 70.6, range 55–106.2) [9]. Baseline examination was performed between 1990 and 1993.

We excluded people with dementia ($n = 482$) [10] or unknown mental state ($n = 455$) and those who could not give an adequate fall history at baseline ($n = 118$). During baseline interviews and subsequent physical and laboratory examinations, information was gathered on several relevant parameters such as age, gender, functional performance [11, 12] and blood pressure. A full assessment of medical and psychiatric comorbidity was also performed. Systolic and diastolic blood pressures were measured in a recumbent position, followed by subsequent measurements in an upright position after 1–5 min of standing. Orthostatic hypotension was defined as a systolic drop of ≥20 mmHg and a diastolic drop of ≥10 mmHg [13]. As exposure of interest we examined the use of drugs. Medication use was determined at baseline by interview and verified by a physician. Drugs were coded according to the Anatomical Therapeutic Chemical classification (ATC) system [14]. Although there is no uniform definition of polypharmacy, we defined it, in accordance with the literature, as the use of four or more medications [3, 5–7]. Drugs associated with falling in the fully adjusted model were classified as risk drugs. As the primary outcome we studied falling. A faller was defined as an individual with a history of one or more falls, without precipitating trauma (e.g. car accident or sports injury), in the 12 months preceding the baseline interview. Falling was assessed by structured personal interviews by trained research nurses.

The Medical Ethics Committee of the Erasmus MC, Rotterdam, the Netherlands, approved the study.

Analysis

We analysed the association between risk factors and falling by means of multivariate logistic regression analysis. We performed an adjusted multivariate analysis adding all known risk factors for falling: age, gender, alcohol use, history of diabetes mellitus, myocardial infarction, hypertension, Parkinson's disease, stroke, thyroid diseases, depressive episodes, functional performance (described as disability index), dizziness, gait disturbance, home-bound life style, joint complaints, memory complaints, orthostatic hypotension, systolic and diastolic blood pressure after 5 min, postural disturbance and visual acuity. All analyses were performed using SPSS version 11.0.1 (SPSS Inc., Chicago, IL, USA; 2001).

Results

A total of 6928 subjects (87%) were eligible for our study, of whom 1144 (16.5%) experienced one or more falls in the previous year. The prevalence of falls strongly increased with age. Falls were more common in women than in men. In addition, fall risk increased with increasing disability, staying indoors because of health, joint complaints, dizziness, gait or postural disturbance, orthostatic hypotension, history of diabetes mellitus, hypertension, Parkinson's disease, stroke, depressive episodes and presence of memory complaints (Table 1). Almost 72% ($n = 4983$) of the participants were taking at least one drug, and 20.3% ($n = 1407$) were taking four or more drugs. The risk of falling increased significantly with the number of drugs used per day (P for trend <0.001) (Figure 1). In the univariate analysis, 28 drugs were associated with falling and were therefore considered as potential risk drugs (Table 2). After adjustment for age, gender, comorbid conditions and disability, falling remained associated with the use of central acting antiobesity products, calcium preparations, potassium sparing diuretics, oxicams, quinine and derivatives, anilides, anxiolytics-benzodiazepine derivatives, hypnotics-benzodiazepine derivatives (Table 2). These drugs were considered as risk drugs.

The probability of using a risk drug increased proportionally with the total number of medications taken, from 25% with the use of only one prescription daily to more than 60% when six or more drugs were prescribed (Figure 2). Women were using significantly more risk drugs than men [odds ratio (OR) 2.2, 95% confidence interval (CI) 1.9, 2.4]. After adjustment for comorbid conditions and disability, polypharmacy (i.e. the number of drugs) remained a significant risk factor for falling. The ORs increased from 1.4 (95% CI 1.0, 2.0) using three medications to 1.6 (95% CI 1.1, 2.1), using four or more medications (P for trend =0.008). Considering the influence of the number of risk drugs, the ORs increased by 42% per risk drug (P for trend <0.001), from 1.3 (95% CI 1.0, 1.6) using one risk drug to 2.5 (95% CI 1.7, 3.6) using two risk drugs. The analysis was also done separately for persons

Table 1
Patient characteristics and risk of falling (n = 6928)

Characteristic	(n = 5784) Without fall n	% (SD)	(n = 1144) With fall n	% (SD)	Odds ratio*	(95% CI)
Age category (years)						
55–64	2302	39.8%	280	24.5%	1.00	Ref
65–74	2141	37.0%	365	31.9%	1.42	(1.20,1.68)
75–84	1080	18.7%	343	30.0%	2.52	(2.11, 3.00)
> 85	261	4.5%	156	13.6%	4.31	(3.40, 5.46)
Mean age (SD)	68.6	(8.6)	73.2	(9.8)		
Female gender	3262	56.4%	868	75.9%	2.43	(2.10, 2.81)
Staying indoors	242	4.2%	169	14.8%	2.19	(1.74, 2.76)
Disability index						
Not disabled	4574	79.1%	595	52.0%	1.00	Ref
Mildly disabled	815	14.1%	272	23.8%	2.02	(1.70, 2.40)
Moderately disabled	254	4.4%	145	12.7%	2.93	(2.29, 3.74)
Severe disabled	141	2.4%	132	11.5%	4.53	(3.38, 6.07)
Alcohol use	2346	40.6%	344	30.1%	0.98	(0.84, 1.16)
Joint complaints	2789	48.2%	701	61.3%	1.51	(1.32, 1.73)
Visual acuity						
Both eyes intact	3860	66.7%	608	53.1%	1.00	Ref
One eye impaired	884	15.3%	203	17.7%	1.11	(0.92, 1.34)
Both eyes impaired	633	10.9%	236	20.6%	1.23	(0.99, 1.52)
Dizziness	1657	28.6%	557	48.7%	1.98	(1.74, 2.27)
Gait disturbance	318	5.5%	181	15.8%	2.47	(1.99, 3.07)
Postural disturbance	149	2.6%	87	7.6%	2.17	(1.62, 2.91)
Orthostatic hypotension†	44	0.8%	22	1.9%	2.10	(1.23, 3.61)
History of diabetes mellitus	328	5.7%	96	8.4%	1.29	(1.01, 1.65)
History of heart attack	523	9.0%	101	8.8%	1.01	(0.80, 1.28)
History of hypertension	804	13.9%	214	18.7%	1.25	(1.05, 1.50)
History of Parkinson's disease	28	0.5%	24	2.1%	3.27	(1.84, 5.82)
History of stroke	192	3.3%	83	7.3%	1.89	(1.43, 2.51)
History of thyroid diseases	477	8.2%	137	12.0%	1.17	(0.95, 1.45)
History of depressive episodes	1769	30.6%	435	38.0%	1.30	(1.13, 1.50)
Memory complaints	1007	17.4%	299	26.1%	1.49	(1.28, 1.74)

**Adjusted for age and gender. †Orthostatic hypotension was defined as a systolic drop of ≥20 mmHg, and a diastolic drop of ≥ 10 mmHg.*

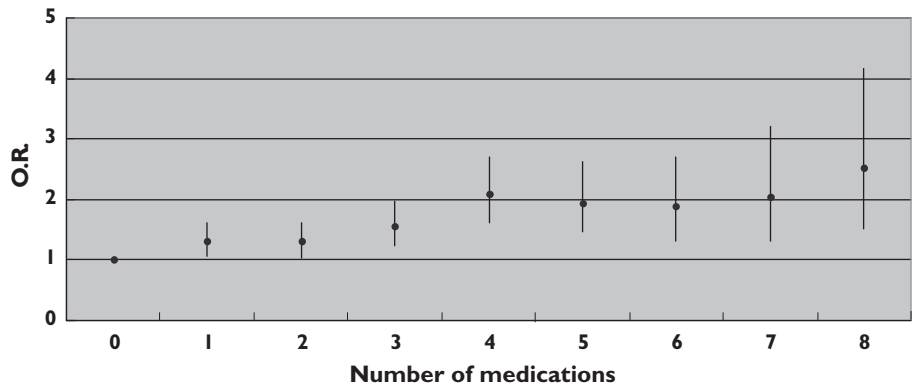

Figure 1
Influence of the number of medications on falling adjusted for age & gender (p for trend <0.001)

Table 2
Drugs associated with falling

ATC code	Description	Cases	Percent cases within users	OR*	(95% CI)	OR† (adj.)	(95% CI)
A	*Alimentary tract and metabolism*						
A06AB	Contact laxatives	26	37.1%	1.8	(1.1, 3.0)	1.3	(0.6, 2.9)
A06AG	Enemas	5	83.3%	23.4	(2.6, 207.8)	0,0	(0.0, ∞)
A08AA	Central acting antiobesity products	7	58.3%	7.7	(2.4, 24.8)	4.9	(1.0, 24.7)
A10BB	Sulphonamides urea derivatives	60	26.2%	1.5	(1.1, 2.0)	1.4	(0.7, 3.1)
A11BA	Multivitamins	19	30.2%	2	(1.1, 3.5)	2.0	(0.9, 4.2)
A11EA	Vitamin b complex	82	26.8%	1.5	(1.1, 2.0)	1.2	(0.8, 1.7)
A12AA	Calcium preparations	36	33.6%	1.9	(1.3, 2.9)	1.9	(1.0, 3.3)
B	*Blood and blood-forming organs*						
B03AA	Oral ferro preparations	24	46.2%	2.8	(1.6, 5.0)	2.3	(0.8, 6.7)
B04AD	Bile acid sequestrants	6	42.9%	3.8	(1.2, 11.8)	2.3	(0.4, 13.5)
C	*Cardiovascular system*						
C03BA	Diuretics—sulphonamides	26	31.0%	2.1	(1.3, 3.4)	1.4	(0.7, 2.9)
C03DB	Diuretics—potassium-sparing agents	18	36.7%	1.9	(1.0, 3.5)	3.6	(1.1, 11.8)
C04AE	Ergot alkaloids	7	50.0%	3.3	(1.1, 9.7)	2.0	(0.4, 9.9)
C05CA	Bioflavonoids	5	50.0%	5	(1.4, 17.9)	3.3	(0.8, 14.6)
G	*Genitourinary system and sex hormones*						
G02CB	Prolactine inhibitors	7	70.0%	10.5	(2.6, 43.4)	NA	(0.0, 0.0)
M	*Musculoskeletal system*						
M01AC	Oxicams	18	40.9%	3.1	(1.6, 5.8)	3.2	(1.3, 7.9)
M09AA	Quinine and derivatives	35	35.0%	1.8	(1.2, 2.8)	2.2	(1.2, 4.2)
N	*Nervous sytem*						
N02BE	Anilides	214	20.7%	1.4	(1.1, 1.6)	1.3	(1.0, 1.6)
N03AB	Hydantoin derivatives	9	33.3%	3	(1.3, 7.0)	1.1	(0.2, 5.8)
N04AA	Anticholinergic agents—tertiary amines	3	60.0%	12	(2.0, 73.6)	4.2	(0.2, 80.2)
N04BA	Dopa and dopa derivatives	17	50.0%	3.5	(1.7, 7.1)	0.8	(0.1, 6.7)
N04BB	Adamantane derivatives	7	43.8%	3.2	(1.1, 9.2)	0.3	(0.0, 4.0)
N04BD	Mao-inhibitors type b	8	50.0%	4.6	(1.7, 12.9)	1.9	(0.2, 20.0)
N05BA	Anxiolytics, benzodiazepine-derivatives	132	26.1%	1.5	(1.2, 1.9)	1.3	(1.0, 1.9)
N05CD	Hypnotics benzodiazepine derivatives	147	27.1%	1.3	(1.0, 1.6)	1.6	(1.1, 2.1)
N07CA	Antivertiginous drugs	59	33.0%	1.7	(1.2, 2.4)	1.0	(0.6, 1.7)
R	*Respiratory system*						
R03BB	Parasympathicolytics	21	29.2%	2.6	(1.5, 4.5)	1.1	(0.4, 2.7)
R05CB	Mucolytics	25	26.9%	1.8	(1.1, 2.9)	1.0	(0.4, 2.3)
S	*Sensory organs*						
S01AA	Ocular antibiotics	4	44.4%	4.7	(1.2, 18.1)	5.9	(0.9, 37.1)

**Corrected for age, gender. †Corrected for age, gender, alcohol use, history of diabetes, history of heart attack, history of hypertension, history of Parkinson's disease, history of stroke, history of thyroid diseases, history of depressive episodes, disability, dizziness, gait disturbance, staying indoors because of poor health, joint complaints, memory complaints, orthostatic hypotension systolic and diastolic after 5 min, postural disturbance and visual acuity.*

under and over age 75 years, and by introducing an interaction-term in the nonstratified statistical analysis. We found no statistically significant interaction ($P = 0.698$). In the age group >75 years old there remained an association of using more than four drugs and falling, although this was no longer significant because of lack of power. Respective ORs were 1.58 (95% CI 1.08, 2.29) for persons 55–74 years old and 1.42 (95% CI 76, 2.67) for persons above 75 years old.

Stratification for presence or absence of at least one risk drug disclosed that polypharmacy is a risk factor for falling only if it includes a risk drug (P for trend =0.004; Figure 3). In other words, polypharmacy itself is not a risk factor for falling unless a risk drug is part of the drug regimen.

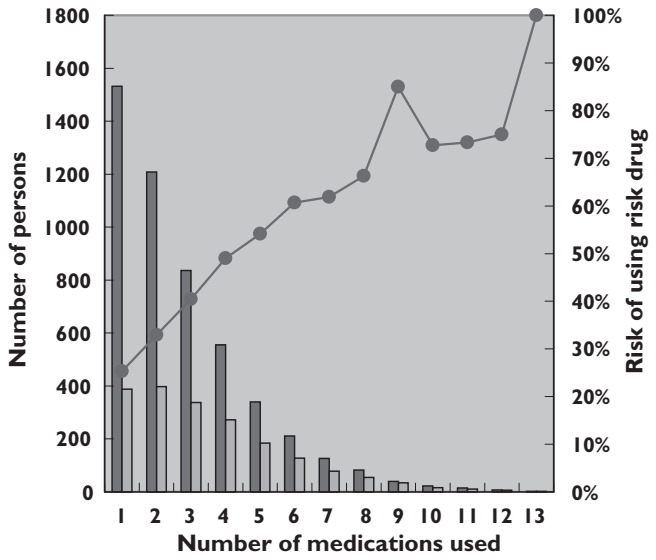

Figure 2
Polypharmacy and use of drugs associated with falling. Users of medications (■), using one or more drugs associated with falling (□), proportion using one or more drugs associated with falling (●)

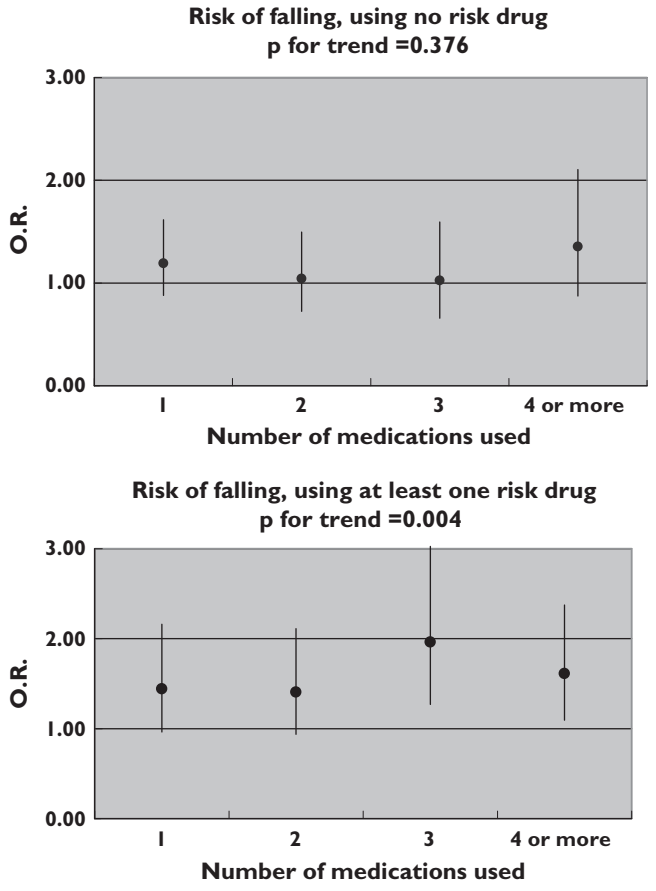

Figure 3
Influence of polypharmacy on falling, stratified on use of risk drugs

Discussion

In this population-based study, fall risk was associated with the use of multiple drugs, but only when at least one established fall risk-increasing drug was part of the daily regimen. Part of the increased risk could be explained by comorbidity as shown in the fully adjusted model, but some drugs appeared to have a risk-increasing effect, independent of comorbidity. This is in contrast to the findings of Lawlor *et al.* [8]. They did, however, study composite groups of medications only. Possible explanations for the mechanism of action are numerous, e.g. diuretics can cause dizziness as a consequence of orthostatic hypotension, with falling as a result. Benzodiazepine derivatives may play a role by effects on the central nervous system. However, after adjustment for comorbid conditions and disability, polypharmacy (i.e. the number of drugs) remained a significant risk factor for falling.

In the Guideline for the Prevention of Falls in Older Persons [2], the assessment of persons having experienced a fall focuses on modifiable risk factors. Our results support the recommendation to assess medication use, being a modifiable risk factor for falling. According to our findings, the falls assessment should focus on identifying risk-increasing drugs rather than polypharmacy *per se* [1].

Limitations of the study

Being a cross-sectional study, our study may have some limitations. First, 37% of our population was younger than 65 years. This possibly explains the relatively low prevalence of falling (16.5%) in comparison with other studies [2], but is consistent with the large study of Lawlor *et al.* [8].

Because of the cross-sectional nature of this study, we cannot be certain that drug use preceded falling. The magnitude of this problem varies between the different observed associations. Calcium preparations, for example, may be prescribed as a consequence of falling to prevent fractures. However, in chronic disease situations, medications are generally prescribed on a continuous basis. Therefore it is likely that most of the drugs were already used before the assessment of falls. Third, it was not possible to control for 'confounding by indication', which is likely to play a role in the association between, for example, calcium preparations or laxative use and falling. Presumably, there is a clinically relevant association between osteoporosis and falling, or between disabling conditions, causing constipation and falling.

The majority of relevant comorbid conditions were taken into account in the analysis. However, we were

not, for example, able to assess the influence of chronic pulmonary diseases on falling. Hence, some residual confounding may play a role in our study. Finally, there may be misclassification of the outcome, which was based on structured interview. The results are dependent upon recall of events, which might introduce 'recall bias' as a consequence of the retrospective character of our study. In an earlier study, falls were recalled with a specificity of 91.4%, and were more likely to be remembered if an injury had occurred. The number of falls was not accurately recalled in more than a third of the persons [15]. In our analysis we therefore dichotomized on falls *vs.* no falls. We have no reason to believe that misclassification of the outcome, if any, was differential. Moreover, the effect of under reporting of falls was minimized by exclusion of persons with an established cognitive disorder, mostly dementia [16].

Potentially, drug interactions can play a role in falling, but the methodology of our analysis was not suitable to address that issue.

Implications

In accordance with the meta-analyses by Leipzig *et al.* [6, 7], we also found an association between diuretics, quinine and derivatives, and psychotropic drugs (especially anxiolytics-benzodiazepine derivatives and hypnotics-benzodiazepine derivatives) with falling.

The major finding of our study is that the contribution of identifiable risk drugs to polypharmacy is associated with an increased fall risk, rather than polypharmacy itself. As a consequence, there is an opportunity for risk-reducing interventions in a frail elderly population, in whom polypharmacy is inevitable in order to control the underlying comorbidity.

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